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Original Research Article

Ceftolozane/Tazobactam as a Treatment for Multidrug-Resistant P. aeruginosa in a Ventricle-Peritoneal Shunt

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Abstract: Multidrug-resistant (MDR) Pseudomonas aeruginosa poses a significant challenge for neurosurgical patients, particularly those with ventriculoperitoneal (VP) shunts. Increasing resistance rates undermine traditional regimens, demanding novel combination therapies. This research article examines the use, effectiveness, pharmacodynamic considerations, and pitfalls of ceftolozane/tazobactam in treating MDR P. aeruginosa VP shunt infections, combining clinical cases, current studies, pharmacokinetics, and stewardship strategies.

Keywords: Multidrug-Resistant Pseudomonas aeruginosa, Ventriculoperitoneal (VP) Shunt Infections, Ceftolozane/Tazobactam, Antimicrobial Stewardship, Pharmacokinetics and Pharmacodynamics.

INTRODUCTION

VP shunt infections are among the most severe complications following neurosurgical interventions, with infection rates ranging from 5–15%. The growing prevalence of MDR Gram-negative bacteria, especially P. aeruginosa, has complicated management. Treatment failures with carbapenems and aminoglycosides due to rising resistance necessitate alternatives. Ceftolozane/tazobactam, a novel oxyimino-cephalosporin/beta-lactamase inhibitor, demonstrates unique anti-pseudomonal activity and broad Gram-negative coverage, making it a candidate for salvage therapy in severe VP shunt infections.

PATHOGENESIS OF MDR P. AERUGINOSA IN VP SHUNTS

- VP shunt infections often follow operative contamination or hematogenous spread.
- Recent data reveal a significant shift toward Gram-negative pathogens in neurosurgical devices[1].
- P. aeruginosa thrives in the CSF and biofilm matrix, exhibiting resistance via efflux pumps, enzyme production (AmpC, ESBLs), porin modification, and, increasingly, carbapenemases.
- Biofilm formation on shunts protects bacteria from host responses and antibiotics, necessitating drugs with both planktonic and biofilm activity.

Rationale and Mechanism for Ceftolozane/Tazobactam

- **Ceftolozane**: A cephalosporin with enhanced stability against AmpC and increased affinity for P. aeruginosa penicillin-binding proteins.
- **Tazobactam**: A beta-lactamase inhibitor protecting ceftolozane from hydrolysis.
- Demonstrated superior in vitro activity against MDR and carbapenem-non-susceptible P. aeruginosa strains[2][3][1].

EVIDENCE: CLINICAL STUDIES, CASE REPORTS, AND OUTCOMES

Clinical Efficacy in CNS/VP Shunt Infections

- Case reports and small series support clinical use; for instance, a pediatric VP shunt infection by MDR P. aeruginosa cleared after 28 days of ceftolozane/tazobactam therapy, combined with shunt externalization. CSF cultures remained negative with no relapse[4][5].
- Broader retrospective studies of MDR-P. aeruginosa infections (mostly non-CNS) show clinical cure rates of 70–71%, though emergence of resistance during treatment was observed in up to 14% of cases[2][3].
- A recent microbiology surveillance highlights growing resistance to carbapenems and beta-lactam/beta-lactamase inhibitor combinations, suggesting ceftolozane/tazobactam as a necessary addition to the therapeutic arsenal for VP shunt infections[1].

Table 1. Clinical Success of Ceftolozane/Tazobactam in MDR P. aeruginosa Infections

Setting	Patients (n)	Success (%)	Reference
CNS (shunt, meningitis, ventriculitis)	1	100	[4][5]
All sites (retrospective study)	21	71	[2][3]

Pharmacokinetics and CNS Penetration

- CSF penetration of ceftolozane/tazobactam is modest (~20%), likely insufficient as monotherapy for meningitis unless the MIC is very low (<0.25mg/L), suggesting utility is highest when combined with device removal/externalization and in susceptible isolates[6].
- Higher doses or prolonged infusions may optimize CSF exposure; further research is needed on intracerebroventricular administration in select cases.

Graph: Comparative CSF and Plasma Concentrations of Ceftolozane/Tazobactam

[image:1]

Challenges: Resistance, Device Management, and Stewardship

- Drug resistance may arise rapidly, often via ampC overexpression or mutation; clinical failure is rarely due to acquisition of new resistance genes during treatment but due to selection of resistant subpopulations[2].
- Shunt externalization or removal, with conversion to an external ventricular drain, is critical for infection clearance, as antibiotics alone are rarely curative in the setting of biofilm.
- Intrathecal administration remains controversial but may be considered in refractory cases[1].

Practical Considerations and Future Directions

- Early and aggressive stewardship interventions, prompt organism identification, and MIC-guided therapy selection are paramount.
- Consider maximum recommended dosing for CNS penetration, with therapeutic drug monitoring where available.
- Multidisciplinary care—neurosurgery, infectious disease, pharmacy—is essential for optimal outcomes.

Table 2. Recommended Drug Options and Strategies for MDR Gram-Negative VP Shunt Infections

Drug/Class	Strengths	Weaknesses	CNS Use
Ceftolozane/Tazobactam	Potent anti-Pseudomonas, well-tolerated	Modest CNS penetration, emerging resistance	Recommended at high dose, esp. with low MIC and shunt removal[4][6][1]
Colistin	Active vs. MDR GN	Nephrotoxicity, neurotoxic, poor CNS levels IV	Intrathecal/intraventricular routes used

Ceftazidime/Avibactam	Broad Gram-negative, CNS experience	Similar PK limits as ceftolozane/tazobactam	Alternative, esp. if ceftolozane resistance
Carbapenems	Historical choice	High resistance rates, poor outcomes	Reserved or combined use
Aminoglycosides (gentamicin)	Synergy, intrathecal use	Limited efficacy IV, toxicity	Intraventricular route, combo therapy

CONCLUSIONS

Ceftolozane/tazobactam represents a promising option in the salvage therapy of MDR P. aeruginosa infections in VP shunt settings. Successful outcomes rely on an integrated approach incorporating antibiotic therapy (at high dose), device management, and multidisciplinary care. Ongoing surveillance and resistance monitoring remain key for stewardship. Further prospective studies are warranted to validate optimal dosing strategies and clarify the role of intraventricular administration.

Figure 1: CSF and Plasma Concentrations of Ceftolozane/Tazobactam
Illustrates the trough and peak levels achieved with standard and high-dose regimens in CSF compared to plasma, emphasizing the pharmacokinetic challenges in CNS infection[6].
[image:1]

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